IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Gorringe, *et al.*
Title:	Modified Whole Cell, Cell Extract and OMV-based Vaccines
Appl. No.:	10/575,070
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Examiner:	Duffy, Patricia Ann
Art Unit:	1645
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Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

DECLARATION UNDER 37 CFR § 1.132

Sir:

I, Dr Andrew Gorringe, do hereby declare and state as follows:

I am currently employed at Health Protection Agency, Porton Down, Salisbury, Wiltshire, UK, SP4 0JG, as a Scientific Leader. I am also an inventor on the present application (US 10/575,070).

I have been actively undertaking research in the technical field of meningococcal disease vaccines for over **18** years. I am responsible for several projects concerned with vaccines against meningococcal disease, including vaccines based on *Neisseria* outer membrane vesicles. A copy of my c.v. is attached showing further details of my academic and research experience.

I am familiar with the prosecution history of US 10/575,070 and have read the Office Action dated 1 September 2009.

In this Declaration, I confirm that the specification as filed describes outer membrane vesicles (OMVs) of *N. meningitidis, N. gonorrhoeae* or *N. lactamica* that have a reduced content of *Neisseria* Opa protein that binds human CEACAM1.

I also confirm that, based on the teaching in the specification and the common general knowledge of a skilled person at the filing date of the application, it would be a matter of routine for a skilled person to prepare the recited OMVs having a reduced content of *Neisseria* Opa protein that binds human CEACAM1.

Description of OMVs having a reduced content of *Neisseria* Opa protein that binds human CEACAM1

The specification as filed provides numerous disclosures of OMVs from *N. meningitidis, N. gonorrhoeae* or *N. lactamica* that have a reduced content of *Neisseria* Opa protein that binds human CEACAM1.

I refer in this regard to page 3, lines 7-21, and to page 4, lines 1-5 and 11-13 – these passages confirm that the OMVs of the invention are from *Neisseria* that are either (i) selected to be substantially free of Opa that binds CEACAM1, or (ii) modified (eg. by mutation) so as to be substantially free of Opa that binds CEACAM1.

Page 5, lines 20-21, and page 10, lines 31-32 also describe OMVs of the invention having a reduced content of (or being free of/ lacking) Opa protein that binds human CEACAM1.

By way of example, as discussed on page 4, lines 15-17, the Opa content of the OMVs may be reduced by at least a factor of 10, as compared with the Opa content of OMVs from 'normal' *Neisseria.* This passage also confirms that a conventional 'benchmark' for the Opa content of normal Neisseria is the Opa content of OMVs from *N. meningitidis* strain K454.

Page 4, lines 18-19 (and page 8, lines 13-17) discusses suitable maximum levels of Opa in the OMVs of the invention. For example, in a specific embodiment, the Opa content in the OMVs of the invention represents 0.5% or less by weight of the total protein content of the OMVs.

As mentioned above, the specification also describes *Neisseria* OMVs that comprise Opa that does not bind CEACAM1. Non-hCEACAM1-reactive Opa proteins may occur naturally in some *Neisseria* strains, or may be produced by recombinant *Neisseria* strains that express a mutated Opa gene.

I refer in this regard to the passages in the specification as filed on page 4, lines 21-23; page 5, lines 21-29; page 6, lines 12-25; and page 12, lines 10-20.

As confirmed in the specification on page 6, lines 27-30, and page 12, lines 12-15, *Neisseria* species are generally amenable to genetic modification. Furthermore, as the entire *N. meningitidis* and *N. gonorrhoeae* genome sequences were available prior to the present application, the information required to generate a *Neisseria* mutant was part of the common general knowledge of a skilled person at the filing date. Suitable conventional genetic engineering techniques are described on pages 6-7 of the specification.

I also refer to the Examples of the specification (as illustrated in the Figures), which confirm that the human CEACAM1-reactive Opa content is reduced in the OMVs of the invention, as compared with the human CEACAM1-reactive Opa content of 'normal' *Neisseria* OMVs.

In this regard, Example 1 of the specification describes experiments using human T cells (ie. expressing human CEACAM1), OMVs obtained from *N. meningitidis* and *N. lactamica*, and OMVs obtained from a number of *N. gonorrhoeae* strains expressing different Opa variant proteins. The variant *N. gonorrhoeae* strains include strain N302 (Opa –ve), strain N303 (expresses

Opa_{50}, which is specific for the receptor HSPG) and strain N309 (expresses Opa_{52}, which is specific for human CEACAM1).

The results are illustrated in Figures 1-5.

Figure 1 shows scanning electron micrograph images of OMVs from *N. meningitidis* (Fig 1A) and *N. lactamica* (Fig 1B).

Figure 2A of the specification shows an immunoblot using an Opa-specific antibody that recognises all Opa proteins. Opa protein was identified in the *N. meningitidis* OMVs, and in the OMVs from Opa-containing *N. gonorrhoeae* strains (illustrated by black bands), but Opa protein was not detected in OMVs the Opa –ve *N. gonorrhoeae* strain N303, or in OMVs from *N. lactamica*.

Figure 2B shows the results of an ELISA assay quantifying interactions between *Neisserial* OMVs and soluble human CEACAM1. Relative binding was calculated based upon mean values for wells incubated with *N. meningitidis* OMVs (100% binding) versus negative control wells with no OMVs (0%). In each instance, the error bars indicate the standard deviations based upon these values from the three replicate wells. OMVs containing Opa protein that binds human CEACAM1 would be expected to show higher relative binding than OMVs that do not contain (or have reduced levels of) Opa protein that binds human CEACAM1.

The results in Figure 2B demonstrate binding between human CEACAM1 and the *N. meningitidis* OMVs. Human CEACAM1 also binds to *N. gonorrhoeae* OMVs comprising Opa_{52}.

However, only background levels of binding are shown for the *N. lactamica* OMVs, the *N. gonorrhoeae* OMVs comprising non-CEACAM1-reactive Opa_{50}, and the *N. gonorrhoeae* OMVs that are Opa –ve. In this type of assay, some non-specific background binding is expected, in the region of 20-30%. I confirm that the level of binding shown for these OMVs is within the confidence intervals of the negative controls.

Figure 2C provides further confirmation that human T cells (ie. expressing human CEACAM1) bind OMVs comprising hCEACAM1-reactive Opa_{52}, but do not bind OMVs comprising non-hCEACAM1-reactive Opa_{50}, or OMVs that are Opa –ve.

Thus, the results presented in Figure 2A, 2B and 2C confirm that OMVs from Opa –ve *N. gonorrhoeae*, OMVs from *N. gonorrhoeae* variants expressing non-CEACAM1-reactive Opa_{50}, and OMVs from *N. lactamica* bind hCEACAM1 at merely background levels as compared with the hCEACAM1-binding ability of OMVs from 'normal' *N. meningitidis* and *N. gonorrhoeae* that express hCEACAM1-reactive Opa protein.

Figure 3 of the specification illustrates the proliferation of human T cells (ie. expressing human CEACAM1) in response to *Neisseria* OMVs in the presence of various cytokine stimuli.

Statistically significant differences in T cell proliferation were seen in the presence v. absence of OMVs comprising hCEACAM1-reactive Opa. In this regard, proliferation of stimulated T cells was significantly inhibited in the presence of OMVs from normal *N. meningitidis* and in the presence of OMVs from *N. gonorrhoeae* that express hCEACAM1-reactive Opa_{52} protein. The observed inhibition of T cell proliferation was significantly reduced in the presence of OMVs from *N. lactamica* or OMVs from *N. gonorrhoeae* strains lacking Opa, or containing Opa that does not bind to hCEACAM1.

The results presented in Figure 3 confirm that eliminating (or reducing the content of) hCEACAM1-reactive Opa protein from *Neisseria* OMVs statistically significantly reduces the inhibition of T cell proliferation that is seen in response to 'normal' *Neisseria* OMVs comprising hCEACAM1-reactive Opa protein.

The results illustrated in Figure 3 are further confirmed by Figure 4, which demonstrates immunosuppression in response to hCEACAM1-reactive Opa

protein (as evidenced by reduced expression of the human T cell activation marker CD69). Exposure to hCEACAM1-reactive OMVs consistently reduced the proportion of activated T cells expressing CD69 (as compared with exposure to hCEACAM1-non-reactive OMVs).

I would also mention that the Figures of the specification have since been published in the accompanying publication by Lee *et al.*, 2007 (see Figures 1-3 of Lee *et al.* and discussion thereof on pages 4451-4453).

Examples 2 and 3 of the specification describe conventional techniques suitable for preparing mutant Neisseria that do not comprise (or have a reduced level of) hCEACAM1-reactive Opa protein. A suitable conventional technique for preparing Opa –ve mutant *Neisseria* is described in Example 4 of the specification. Example 6 of the specification also describes suitable routine techniques for screening and generating non-hCEACAM1-reactive Opa variants.

I therefore confirm that the specification as filed provides a clear and complete written description of the OMV compositions recited in the pending claims, which have a reduced level of hCEACAM1-reactive Opa protein.

Feasibility of making and using OMVs having a reduced content of *Neisseria* Opa protein that binds human CEACAM1

I confirm that a skilled person reading US 10/575,070 as filed would face no 'undue burden' in preparing and using the OMVs recited in the claims.

In this regard, the Examiner is incorrect to allege that *Neisseria* express a 'vast array' of Opa variants.

There are only 4 Opa loci in meningococci (OpaA, OpaB, OpaD and OpaJ) and 11 Opa loci in gonococci. It is true that variants of these Opa proteins occur. However, as confirmed in the accompanying publication by Callaghan *et al.* (2008), the variation is confined to specific variable regions of the Opa

genes, and the majority of residues in the Opa gene sequences are conserved (see Figure 1 of Callaghan *et al.*).

I therefore confirm that a skilled person in this field would not consider the total number of *Neisseria* Opa loci to be 'vast'.

I note that the claims have been amended to focus on OMVs obtained from 3 well-characterised *Neisseria* species – namely, *N. meningitidis*, *N. gonorrhoeae* and *N. lactamica*. The entire *N. meningitidis and N. gonorrhoeae* genome sequences were in the public domain prior to the filing date of this application. Hence, a skilled person would have no difficulty in identifying the Opa loci of these *Neisseria* species or from *N. lactamica* using homology to the meningococcal or gonococcal genes.

Furthermore, it would be a matter of routine for a skilled person to prepare OMVs from *N. meningitidis*, *N. gonorrhoeae* and *N. lactamica* that have a reduced content of Opa protein that binds CEACAM1.

In this regard, it is very feasible to knock out 4 genes from a meningococcus (or 11 genes from a gonococcus). A skilled person would be able to knock out any *N. meningitidis*, *N. gonorrhoeae* or *N. lactamica* OpaJ protein, because the skilled person knows the sequence of the conserved regions of the OpaJ sequences.

As discussed above, Examples 2-4 and 6 of the specification describe suitable conventional methods that a skilled person would be able to use, as a matter of routine, to produce *Neisseria* mutants (and hence OMVs) having reduced levels of hCEACAM1-reactive Opa.

Example 4 of the specification refers to 2 papers by Cornelissen, which describe preparation of knock-out mutants of *Neisseria* (Cornelissen *et al.*, 1992 and Cornelissen and Sparling, 1996 – copies enclosed). The gene that is 'knocked-out' in these publications is transferrin-binding protein (tbp) –

however, as would be appreciated by skilled person, this technique is applicable to any *Neisseria* gene.

Another conventional technique that a skilled person would have used at the filing date to prepare knock-out *Neisseria* mutants is described in the accompanying publication by Li *et al.*, 2009 (see "Materials and Methods" section headed "Construction of the NMB1966 mutant"). Again, I confirm that this technique is applicable to knocking out any *Neisseria* gene.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Signed ..... A. R. Gorringe ..... A.R. GORRINGE

Witnessed .... T. ALEXANDER

Dated ..... 1st December 2009 .....

CURRICULUM VITAE.

Name:	Andrew Richard **GORRINGE**.
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Address:	Health Protection Agency, Centre for Emergency Preparedness and Response, Porton Down, Salisbury SP4 0JG, UK

Education and Qualifications.

1983-88 University of Southampton, Faculty of Medicine, Department of Microbiology.Awarded Ph.D. in April 1988 for the thesis "The effects of growth conditions on the expression of virulence determinants of *Bordetella pertussis*".

1977-81 University of Bath, School of Biological Sciences.
Degree: B.Sc.(Hons) in Applied Biology, Specialising in Microbiology.
Classification: Upper second class.

Employment

Currently Scientific Leader, Health Protection Agency Centre for Emergency Preparedness and Response (CEPR), Porton Down, Salisbury SP4 0JG, UK (formerly, Centre for Applied Microbiology and Research, CAMR)

Sept 1981 Member of acellular pertussis vaccine research team, CAMR
April 1989 Senior Grade Microbiologist, Bacterial Antigens Group. CAMR
July 1990 Clinical Scientist, Grade B, Leader, Meningococcal Antigens Project, April 1997 Project Team Leader, Bacterial vaccines, CAMR
April 1999 Meningococcal Vaccines Group Leader, CAMR.
April 2003 Meningococcal Vaccines Group Leader, Health Protection Agency, Porton Down.
Nov 2008 Scientific Leader, CEPR

- Member of the MRC College of Experts. 2004-present
- Member of the Health Protection Agency Meningococcus Forum. 2001-present
- Visiting Lecturer, University of Bath, Department of Biology and Biochemistry. 1994-present
- Member of the Society for General Microbiology. 1989- present
- Member of the Scientific Committee for the International Pathogenic *Neisseria* Conference 2002.

Distinctions/Honours

American Society for Microbiology ICAAC Program Committee Award, 2000.
Honorary member, Cuban Society for Immunology.

Relevant courses

Attended the Fondation Mérieux 5th Advanced Vaccinology Course, Annecy May 2004. The course is taught by leading figures in the vaccinology field and aims to facilitate critical decision making in vaccinology by providing participants with a comprehensive overview of the field, from immunology to vaccine development and clinical trials and the social, economic, political and ethical issues of vaccination.

Research interests

I have been involved in bacterial vaccine projects during 28 years CAMR and CEPR. Initially, I worked in the team that developed an acellular pertussis vaccine that was assessed in phase I and phase II clinical trials. More recently, I have led projects to identify and characterise antigens that will be effective in a vaccine against serogroup B meningococcal disease. This research has focused on meningococcal transferrin binding proteins and more recently has included projects to assess the vaccine potential of *Neisseria lactamica*. A novel vaccine based on *N. lactamica* outer membrane vesicles was developed from first laboratory proof of concept to cGMP manufacture and a Phase I clinical trial. A major focus of current research is the development of new assays for assessment of meningococcal vaccines, particularly an opsonophagocytosis and other flow cytometry-based assays. I am also engaged in pertussis vaccine research to determine the role of fimbriae in protective responses

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